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Metastatic Primitive Neuroectodermal Tumour of the Ovary: Successful Treatment With Mega-Dose Chemotherapy Followed by Peripheral Blood Progenitor Cell Rescue

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Primitive neuroectodermal tumours (PNET) of the ovary are rare, aggressive tumours which are associated with high morbidity and mortality. Previously reported cases have shown limited response to therapy in patients presenting with metastatic disease and survival rates have been discouragingly low. We report the case of a 13-year-old girl who presented with a primary ovarian PNET and extensive metastatic disease. Pathologic studies confirmed the neural origin of the tumour and its morphologic appearance of neuroblastoma. Incomplete surgical resection was followed by treatment with aggressive multi-agent chemotherapy including cis-platinum, etoposide, cyclophosphamide, anddoxorubicin as per a neuroblastoma treatment protocol. Complete clinical remission ensued and she received consolidative therapy with myeloablative doses of thiotepa, melphalan, and carboplatin followed by autologous peripheral blood progenitor cell rescue. All therapy was well tolerated and the patient remains in complete remission with no evidence of disease 18 months from presentation. Mega-dose chemotherapy followed by progenitor cell rescue may provide optimal therapy for patients presenting with metastatic ovarian PNET. Med. Pediatr. Oncol. 29:308–312, 1997.

Key words: ovary; primitive neuroectodermal tumour; chemotherapy; autologous progenitor cell transplant

INTRODUCTION

Ovarian teratomas often comprise elements of neurally derived tissue. However, ovarian tumours which can be classified pathologically as primary neuroectodermal tumours are rare. These are often very aggressive tumours and are associated with a high mortality [1].

We report a case of metastatic primitive neuroectodermal tumour (PNET) of the ovary, successfully treated with mega-dose chemotherapy followed by autologous peripheral blood progenitor cell (PBPC) rescue.

CASE REPORT

History

A 13-year-old post-menarchal girl presented with low-grade, intermittent fevers, vague abdominal pain, diarrhea, and weight loss. Physical examination revealed an unwell looking girl with obvious abdominal ascites and evidence of respiratory compromise.

Investigations

Investigations revealed abnormally high serum LDH and Ca 125 levels and elevations in 24-hour urinary VMA (vanillyl methoxymandelic acid) and norepinephrine excretion. Serum calcium, alpha-fetoprotein, and beta-human chorionic gonadotropin levels were normal.

Radiographic investigations showed a large abdominal tumour arising from the pelvis and extending to the liver and into the pouch of Douglas. Large bilateral pleural effusions, a pericardial effusion, mediastinal adenopathy, and pleural and pericardial deposits of tumour were also identified. Bone marrow aspiration and biopsy and nuclear medicine bone scan were negative for metastatic disease.

Surgery

At laparotomy there was a huge right-sided ovarian tumour along with extensive peritoneal seeding and massive infiltration of the omentum. The uterus was nor-

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mal. The surface of the left ovary was studded with tumour. In view of the extent of diffuse intraperitoneal disease, gross total resection was not feasible and a right salpingo-oopherectomy and omentectomy were performed.

Pathology

The ovarian tumour consisted of a large, oval-shaped mass weighing 1448 grams. The cut surface showed a yellowish-tan tissue with numerous small and large nodules. The omental-tissue was studded with similar-appearing tumour tissue and weighed 1855 grams. Histology showed virtually complete replacement of the ovary by nests and cords of primitive malignant small blue cells with coarse chromatin and one or more distinct nucleoli. The cells showed very little evidence of differentiation, resembling those observed in primitive forms of neuroblastoma, including the formation of neural rosette-like structures (Fig. 1A). In other areas neural differentiation was more overt, with ganglion cells and a neurophil background being evident (Fig. 1B). Immunohistochemical analysis revealed strong staining for neuronal neurofilament, characteristic of primitive neural cells, and focal positivity for neuron-specific enolase, synaptophysin, and glial fibrillary acidic protein (GFAP). Staining for chromogranin, desmin, muscle-specific actin, cytokeratin, alpha-fetoprotein, leukocyte common antigen, and the Ewing sarcoma marker O13 were negative. Ultrastructural analysis revealed primitive cells with neural processes and microtubule formation, but dense core granules were not identified. Cytogenetic analysis failed to reveal an abnormal clone. Molecular genetic analysis was negative for *EWS/FLI1* and *EWS/ERG* gene fusions characteristic of the Ewing sarcoma family of primitive neuroectodermal tumours [2]. Furthermore, there was no evidence of *MYCN* gene amplification which characterizes a subset of childhood neuroblastoma cases [3]. The final pathologic diagnosis was that of a PNET of the ovary with neuroblastic and focal ganglionic differentiation.

Induction Chemotherapy

Given the histologic appearance of the tumour and the known responsiveness of malignant ovarian germ cell tumours to cisplatinum based regimens [4], the Children's Cancer Group high-risk neuroblastoma protocol, CCG-3891, was followed. The patient received 4 cycles of therapy at q 4 weekly intervals. Each cycle lasted 6 days and consisted of cisplatinum 60mg/m^2 IV day 0, etoposide 100 mg/m^2 IV days 2 and 5, doxorubicin 30 mg/m^2 day 2, and cyclophosphamide 900 mg/m^2 IV days 3 and 4. Complications included hemorrhagic cystitis which was effectively managed with the addition of mesna and prolonged intravenous hydration, mild high frequency hearing loss after the fourth cycle of therapy and a single episode of fever and neutropenia.

Response to Induction Chemotherapy

Response to initial chemotherapy was dramatic. A CT scan of the abdomen after only one cycle of therapy could not identify clear evidence of residual disease. After completion of 4 cycles the patient was in full clinical, biochemical, and radiographic remission.

A second-look laparotomy revealed only minimal residual disease. Multiple biopsies were taken and while small areas of maturing neural tumour were found in the omentum and left broad ligaments, there was no evidence of residual malignancy. (Fig. 2).

PBPC Harvest

The patient subsequently received granulocyte colony stimulating factor (G-CSF) at a dose of 10 micrograms/kg subcutaneously for 7 days and then underwent two apheresis procedures with collection of CD34+ progenitor cells. A total volume of 250ml of cells were collected with a total count of 19.6×10^6 CD34+ cells/kg.

Consolidative Chemotherapy

Five months after her original presentation and one week following progenitor cell harvesting, the patient was treated with myeloablative doses of chemotherapy as per a locally developed protocol. The preparative regimen included carboplatin 1 gram IV daily and thiotepa 250mg/m^2 IV daily for 3 days on day -6, -5, and -4. (Carboplatin dose calculated according to target AUC = 8mg/ml/min) [5]. Melphalan was given on day -3 at a dose of 160mg/m^2. After 2 days of rest, the collected PBPC were reinfused on day 0 and on day +4 G-CSF was begun at a dose of 5μg/kg/d subcutaneously.

The chemotherapy was well tolerated and the PBPC engrafted quickly. Complications of therapy included mucositis, fusiform gram negative rod sepsis, and transient renal dysfunction.

Follow-up

Eighteen months following her presentation and 14 months following completion of therapy the patient is alive and well with no evidence of recurrent disease. The only residual complications of therapy have been high frequency hearing loss and ovarian failure. She is maintained on hormone replacement therapy.

DISCUSSION

It is not uncommon for ovarian tumours to show elements of neuroectodermal differentiation. However, tu-

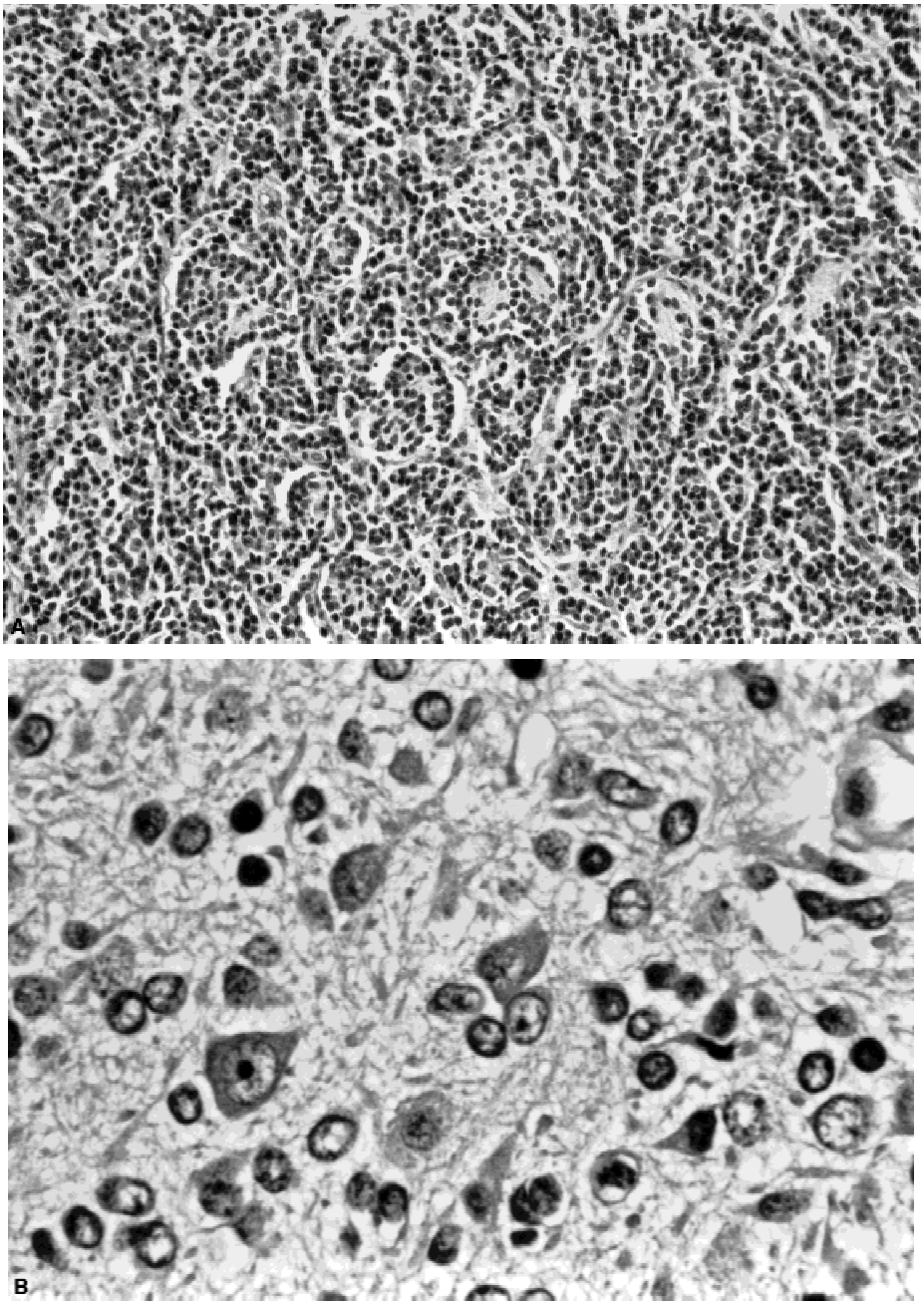

Fig. 1. Histopathology of PNET of the ovary. A. The photomicrograph shows nests and cords of primitive small neuroblastic cells forming occasional neural-type rosettes. B. A higher power shows more overt neural differentiation with ganglionic cells (2 o'clock) in a neuropil background.

mours which are comprised almost solely of neurally derived tissues are rare [6]. In cases of immature ovarian teratomas containing neuroectodermal tissue, there is almost always evidence of mesodermal and endodermal differentiation. Tumours such as the one described in this case report are best classified as a form of monophyletic germ cell neoplasm in the category of monodermal teratomas [7].

Despite this classification, traditional germ cell tumour therapies have proven inadequate in the treatment of ovarian PNETs in the past. A recent review of 25 ovarian neuroectodermal tumours included 12 patients with primitive tumours along with 6 differentiated and 7 anaplastic tumours [1]. The primitive and anaplastic tumours tended to be of higher malignant grade, occurred in younger patients and were associated with a very aggressive course. Pathologic appearance of the 12 primitive tumours included medulloblastoma, medulloepithe-

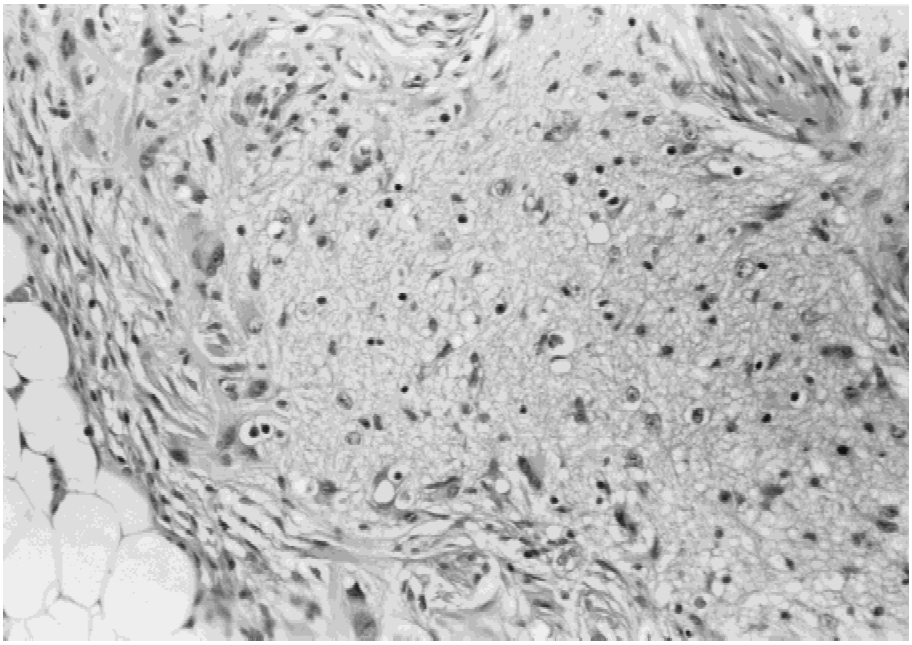

Fig. 2. Histopathology of ovarian PNET after chemotherapy. A nodule of residual tumour shows clear neural differentiation with ganglionic cells (9 o'clock) and Schwannian cells in a neuropil background. Moreover, there was strong immunohistochemical staining in these regions using antibodies to a panel of neural markers including neuron-specific enolase, S100, glial fibrillary acidic protein, and synaptophysin (data not shown).

lioma, ependymoblastoma, and neuroblastoma. All 7 of the patients who presented with metastases had died of their disease or were alive with disease after follow-up of 2–20 months. Treatments in these patients varied but were largely based on germ cell tumour protocols and ranged from surgical resection alone to surgery plus adjuvant chemotherapy and radiation therapy.

A single case report with a four year disease-free survival was reported by Block et al [8]. A 22-year-old woman with metastatic neuroblastoma arising from an immature teratoma responded well to multi-agent chemotherapy and local radiation therapy. Our patient had an equally impressive response to chemotherapy being in full clinical remission following only 4 cycles of therapy. There was very little residual tumour at the time of second-look surgery and pathologically it had undergone ganglionic differentiation. In view of this tremendous response, radiation therapy was not pursued and it was elected to consolidate her treatment with mega-dose chemotherapy followed by PBPC rescue. While there is as yet no published literature to support this therapeutic modality in this type of tumour specifically, its success in the treatment of other chemosensitive solid tumours, including neuroblastoma, may need to be extrapolated to include ovarian PNETs [9,10]. Definitive trials to properly evaluate this question will be difficult in view of the rarity of the tumours.

In summary, ovarian PNET is a very rare and aggressive tumour. Germ cell tumour based regimens have traditionally not been successful and therapy directed at the pathologic subtype of the tumour appears to be more effective. Multi-agent induction chemotherapy followed by consolidation with mega-dose chemotherapy and PBPC rescue was both efficacious and well-tolerated in our patient and may prove to be optimal therapy for all patients with metastatic ovarian PNET.

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